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Review Article

Recent Applications and Evaluation of Metal Nanoparticle–Polymer Hybrids as Chronic Wound Dressings

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Chronic wounds, which include venous leg ulcers, diabetic foot ulcers, and pressure ulcers, are a global health issue that affects between 1% and 2% of the developed world's population. Chronic wound healing necessitates extensive medical intervention at costly healthcare expenses. Wound care management is mainly dependent on the discovery of new and appropriate chronic wound dressing materials, and it remains a focus of research in chronic wound care. Biocompatible metallic nanoparticle-loaded wound dressing offers a novel opportunity for effectively overcoming the inherent drawbacks of traditional wound dressing materials, particularly in overcoming nonhealing chronic wounds due to their clinical complexity, for example, wound infections, chronic irritation, and trauma, persistence of foreign body or bacterial proteins, and ischemia. In this review, we will primarily focus on the advancements in nanoparticle-based antibacterial and antioxidant wound dressing materials (e.g., hydrogels, electrospun scaffolds, sponges, and films) for the treatment of chronic wounds, which overcome the limitations of traditional dressings.

1. Introduction

Skin is the body's most important and largest organ [1]. It completely surrounds the outside of the body and protects us against radiation, mechanical blows, external pressures, temperature changes, microorganisms, and chemicals [2, 3]. Skin wounds (e.g., chemical burns, thermal injuries, cuts, and scratches) have an impact on various skin functions, including neuropathy, bacterial infections, failure of thermoregulation, and so on [4–8]. Wounds are generally classified as acute and chronic [9]. Acute wounds (such as, surgical wounds, traumas, superficial burns, and irradiation) heal in 1–12 weeks, whereas chronic wounds (such as, pressure ulcers, vascular ulcers, and diabetic ulcers) are a significant healthcare burden in the world because they do not heal in the expected time (it takes more than 2 months), are more susceptible to infection, and are more difficult to cure (nonhealing) [10–13]. Normal wound healing is a complicated biological operation in the human body that involves four phases such as hemostasis, inflammation, cell proliferation, and tissue remodeling (Figure 1) [14]. (i) During the hemostasis phase, the body's healing and blood-clotting systems are activated, and a barrier is formed to stop the bleeding. (ii) The inflammatory phase, which kills microorganisms and prepares the wound bed for future tissue formation. (iii) In the proliferation phase, the wound is filled with newly formed tissue, the wound edges are contracted, and the wound is covered with epithelium. (iv) During the remodeling of scar tissue phase, the newly formed tissue becomes stronger and more flexible [15–17].

Due to the complexity of healing chronic wounds, any single therapeutic strategy is unlikely to result in satisfactory recovery. Another important issue is bacterial infection at the wound site, which can delay wound healing and possibly lead to life-threatening putridity. As a result, in chronic wound dressings, it is necessary to design a wound dressing material with antibacterial and enzyme inhibitory capabilities in combination with high hydrophilicity, elasticity, tensile strength, air permeability, and biodegradation in order to restore normal skin integrity and speed up the wound healing process [19, 20]. Currently, there are numerous wound dressings available, including dry gauze, sponge, film, ointment, hydrogel, fiber, solution, and electrospun membrane (scaffold) [21–26]. These various wound dressing materials have been

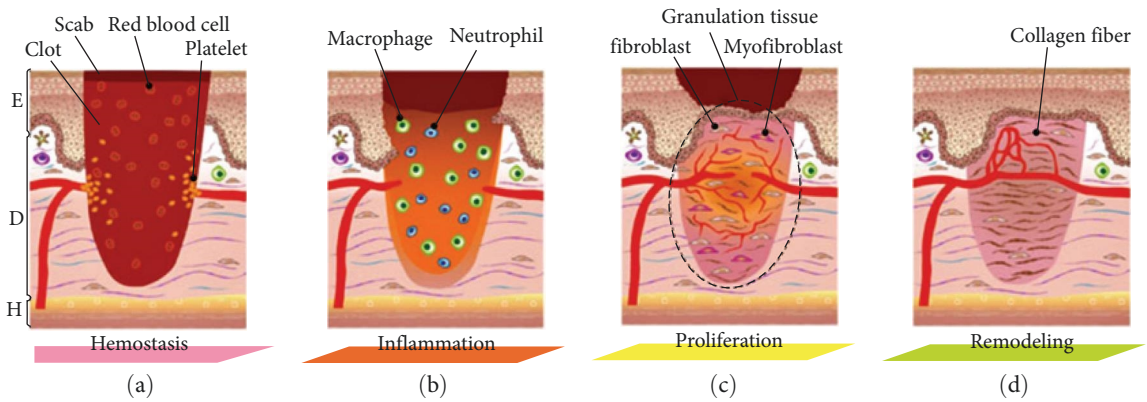

Figure 1: (a–d) Schematic representation of normal wound healing stages [18].

created utilizing a range of materials, including biopolymers such as alginate (ALG), collagen (COL), dextran (DEX), cellulose (CL), gelatin (GEL), and chitosan (CS), as well as synthetic polymers, such as polyvinyl alcohol (PVA) [27]. This review comprehensively presented the purpose and consequences of polymer-based wound dressing materials (e.g., hydrogels, electrospun membrane, film, and sponge) loaded with metallic and metallic oxide nanoparticles (e.g., Ag, Au, ZnO, CuO, CeO_2, and TiO_2) in order to accelerate the healing process of chronic wounds, with the purpose of providing a theoretical reference for chronic wound healing.

2. Polymeric Wound Healing Biomaterials

Various polymers, such as natural polymers (e.g., cellulose, chitosan, hyaluronic acid, gelatin, alginate, and chitin) or synthetic polymers (e.g., polyurethanes, poly(vinyl alcohol), and polylactide), can be utilized to prepare effective and ideal wound healing dressing materials [28, 29]. Polymer-based wound dressings that have been loaded with bioactive agents, nanomaterials, or drugs may have better therapeutic effects, such as strong antibacterial or antioxidant activity [28, 30]. Hybrid-based wound dressings are produced by combining natural and synthetic polymers in the design of wound dressings [31]. Enhanced mechanical capabilities, superior flexibility, quicker wound healing, biodegradability, biocompatibility, and high adsorption capacity are all excellent features of hybrid wound dressings [32].

Collagen (COL) is the most common protein found in animal bones, muscle, and skin [33, 34]. COL is considered one of the most valuable biomaterials for wound dressing due to its great biocompatibility, biodegradability, and minimal antigenicity [35, 36]. However, COL application is limited due to its weak physicochemical and perishable characteristics [37].

Gelatin (GEL) is a solid, colorless, tasteless, and semitransparent substance composed of denatured proteins generated by partial hydrolysis of collagen under specified reaction conditions [38, 39]. Gelatin is most commonly found in the skin and bones of land animals, although it can also be found in fish and pesticides [40, 41]. Due to GEL superior biocompatibility, nonimmunogenicity, biodegradability, cell interactivity, and commercial availability, gelatin is commonly utilized as biomaterial for tissue engineering and other biomedical applications [42–45].

Chitosan (CS) is a linear polysaccharide that is derived from acetyl chitin and is found in the cell walls of anthropoids like crabs and shrimp [46, 47]. CS possesses antibacterial, antifungal, and antiyeast activities, as well as being biodegradable, biocompatible, water absorbent, and nontoxic [48, 49]. It may be even more antimicrobial at lower pH levels. As a result, CS has a great deal of promise for use as a wound dressing for the treatment of skin scars and tissue damage [50, 51]. More significantly, chitosan's capacity to mix with other materials and produce composites with sponge topologies is the polymer's most intriguing feature [52].

Dextran (DEX) is a natural glucose-based polymer with reactive hydroxyl groups that provide hydrophilicity and being able to be manufactured, changed, or functionalized for various medicinal and biological purposes, as well as promising wound dressing due to its excellent antimicrobial activity [53–56]. DEX has been widely explored as a safe biomaterial for the targeted and sustained delivery of drugs, enzymes, and proteins due to its outstanding biocompatibility and biodegradability [57].

Bacterial cellulose (BC) is a type of microbial polysaccharide produced by aerobic bacteria that has distinct physiochemical properties from plant cellulose [58–62]. Due to its great mechanical strength, crystalline nature, biodegradability, biocompatibility, hydrophilic nature, flexibility, nontoxicity, and water retention ability, BC membranes (BCM) are utilized in wound dressings, drug delivery, bone transplants, tissue engineering, artificial arteries, and dental implants [63–66].

Sodium alginate (SA) is a linear polysaccharide and copolymer generated from brown marine algae that is neutral and water soluble [67, 68]. SA's antibacterial and antifungal activity, strong hydrophilicity, outstanding biocompatibility, biodegradability, affordability, and ability to absorb wound exudate make it ideal for application as a polymeric wound dressing [69, 70].

Poly(vinyl alcohol) (PVA) is a mild water-soluble synthetic biodegradable linear polymer that is utilized in a variety of commercial, industrial, medicinal, and dietary applications [71]. PVA is one of the most appealing synthetic polymers for wound dressing application due to its good properties, such as biocompatibility, high mechanical strength, high hydrophilicity, and providing moisture conditions for wound healing applications [72–74]. The same dressing materials are often loaded with various nanomaterials in the most sophisticated designs, such as silver nanoparticles (AgNPs), cerium oxide nanoparticles (CONPs), and others to improve their antibacterial and antioxidant activities, and hence accelerate wound healing [75–77].

3. Nanoparticles for Potential Wound Healing Applications

Nanotechnology has recently provided an excellent approach to enhancing acute and chronic wound healing by encouraging proper mobility throughout the numerous stages of healing [78]. Nanoparticles (NPs) have been highlighted as an effective wound healing therapy technique among all other nanomaterials due to their ability to function as both a therapeutic and carrier system, as well as many other unique properties [79, 80].

Cerium oxide (CeO_2) nanoparticles (CONPs) are employed in a variety of medicinal applications due to their anti-inflammatory, anticancer, and proangiogenic characteristics [76, 81–84]. CONPs-loaded wound dressings have been shown to enhance wound healing in vitro and in normal animal models due to their cell infiltration, antibacterial, and antioxidant/anti-inflammatory activity via the redox interaction between Ce^{3+} and Ce^{4+}, according to recent findings [20, 85–88].

Silver nanoparticles (AgNPs) have gained importance in wound dressing due to their extensive antibacterial activity and ability to meet the requirements for therapeutic resistance [89, 90]. The mechanism of action of AgNPs is unknown, but the most widely accepted theory is that Ag^+ could attach to the bacterial cell wall via interactions between Ag^+ and the thiol part of proteins on the cell membrane, impacting bacterial cell viability by preventing DNA replication [91]. AgNPs, whether in the metallic form (Ag^0), oxides (mostly Ag_2O), or cationic forms (Ag^+), have a strong antibacterial effect [92–95].

Gold nanoparticles (AuNPs) have also been widely used in medicinal and biological applications as a promising antibacterial and antioxidant agent [96]. Certain AuNPs were utilized to improve wound dressings for acute and chronic wounds [97, 98]. However, the preparation and administration of AuNPs in vivo might result in cytotoxicity, and their toxicity is highly correlated with the dosage, size, concentration, and exposure period [99, 100]. As a result, while employing it for biomedical purposes, its possible long-term negative consequences should be carefully evaluated. When employed in certain environments, uncoated AuNPs are sensitive to temperature, pH, electrolyte balance, and solvent, and they are also prone to aggregation, which is a key challenge that must be solved before a nanoparticles can be integrated into a biological molecule [101, 102]. In addition, gold is too expensive to be used as a wound healing material, thus alternative metallic nanoparticles (NPs) with cheaper prices and superior antibacterial properties are used in its stead.

Zinc oxide (ZnO) nanoparticles (ZONPs) are antimicrobial, biocompatible, affordable, nontoxic, and environmentally friendly, which stimulate keratinocytes by releasing Zn ions on the wound surface and hence speeds up wound healing [103–105]. More importantly, the antibacterial activity of ZnO nanoparticles with smaller particle sizes is greater [106]. ZnO contains the micronutrient Zn, which is known to stimulate angiogenesis (the creation of new blood vessels), which leads to tissue repair and recovery [107]. The release of Zn^{2+} ions in aqueous suspension from the breakdown of ZnO particles enhances ZnO's antibacterial activity [108].

Titanium dioxide (TiO_2) nanoparticles (TONPs) have attracted the attention of many researchers among various antibacterial nanoparticles due to their biocompatibility, nontoxicity, strong antibacterial activity, and exceptional physical and chemical stability [109]. TiO_2 has shown high biocompatibility with tissue and blood, making it an attractive material to investigate for a variety of blood-compatible coatings for biomedical applications [110, 111].

Copper NPs (CuNPs) and copper oxide (CuO) nanoparticles (CuO-NPs) show exceptional effectiveness as antibacterial agents, thus accelerating wound healing [112–114]. They serve a complicated role in a variety of cells, control the actions of multiple cytokines and growth factors, producing important growth proteins, and are fundamentally engaged in all four stages of wound healing processes. However, CuNPs and CuO-NPs have demonstrated significant toxicity in numerous investigations, when compared to several other metal and metal oxide nanoparticles [115–118]. Various substances were found to delay the release of copper ions, such as folic acid, reducing cytotoxicity and enhancing cell motility, hence enhancing wound healing process [119].

Strontium nanoparticles (SrNPs) have attracted a lot of attention in recent years due to their distinctive physical and chemical characteristics. SrNPs offer a wide range of uses, including drug delivery, bioimaging, cancer treatment, wound dressings, and more [120]. Personalized SrNPs-loaded scaffolds can be used to accommodate any size dental implant and may aid in patients' healing and tissue attachment [121]. Sr^{2+} ions are also one kind of inorganic angiogenic agent that can promote blood vessel development, according to a study [122]. Thus, their inclusion in wound dressings will promote faster regeneration and accelerate wound healing.

In addition to the metal and metal oxide NPs presented in this prospective, other NPs such as silica NPs (SiNPs), iron oxide NPs (IONPs), cobalt ferrite NPs (Co–FeNPs), and others have gained a lot of attention recently due to their biocompatibility and biodegradation in the biomedical field.

4. Polymer-Based Dressings Loaded with Nanoparticles

4.1. Hydrogels. Hydrogels (hydrophilic gels) are cross-linked polymeric 3D networks that have the capability of absorbing

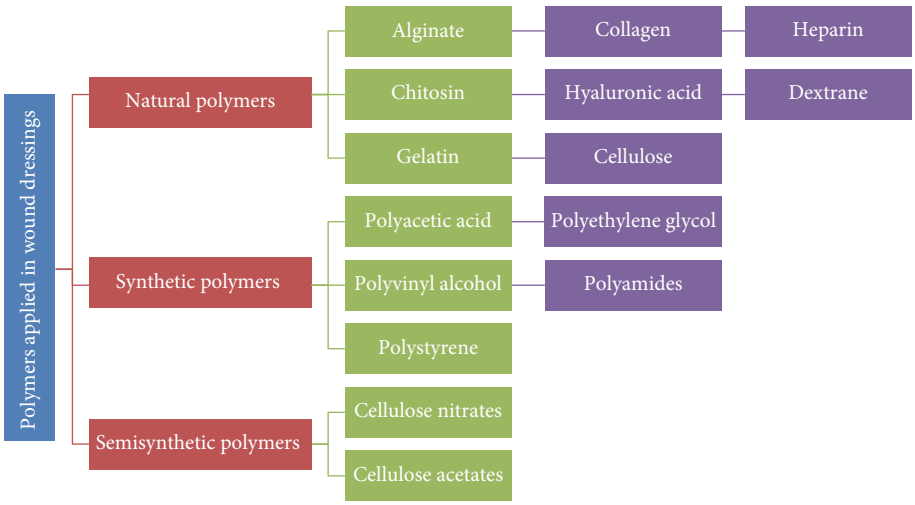

Figure 2: Commonly employed natural and synthetic polymers are used for hydrogel preparation.

a large volume of water (wt. 20%) without dissolving in water (aqueous medium) [123–126]. The presence of hydrophilic functional groups on the polymeric backbone is the reason behind absorption of substantial amount of water, while hydrogen bonding and ionic interaction between polymeric chains (cross-linked structure) help them resist dissolution in aqueous medium [127]. Since the invention of synthetic hydrogels in 1954, natural hydrogels have been ruled out in favor of synthetic hydrogels, which have a higher water absorption capacity, strength, shelf life, and self-healing [124, 128, 129]. Synthetic hydrogels are utilized in wound dressing, medicines, biotechnology, tissue engineering, therapeutic agents, and other biomedical applications [124].

Based on hydrogel's 3D structure, high moisturizing capabilities, good permeability, excellent biocompatibility, and transparency, it is commonly used as wound dressing materials for chronic wound healing [27, 130, 131]. Hydrogels are soft, easy-to-change polymers that absorb wound exudate and clean the wound bed while also reducing wound temperature and calming the wounded area, making them particularly useful in the treatment of dry wounds [132]. As a result, these materials can be used in all four stages of wound healing. However, most hydrogels have been enhanced with various nanomaterials to improve their healing potential such as antioxidant/anti-inflammatory activity and antibacterial activity for chronic wounds.

Natural and/or synthetic hydrophilic polymers are chemically or physically cross-linked to form hydrogels. Figure 2 lists the most often utilized natural and synthetic polymers for hydrogel production [132].

4.1.1. Antioxidant Hydrogels. The antioxidant hydrogel can eliminate excess ROS form chronic wounds, minimizing oxidative stress, enhancing the wound microenvironment, and facilitating potentially rapid wound healing [133]. Low amounts of reactive oxygen species (ROS) promote normal wound healing by encouraging cell migration and angiogenesis, while high levels of ROS can delay or even compromise chronic wound healing [134, 135]. A persistent inflammatory response in chronic wounds results in a massive production of ROS, which surpasses the antioxidant capacity of the cells, preventing the wound from transitioning from the inflammatory to the proliferative phase [133, 136]. Thus, many hydrogel dressings with antioxidant activities have evolved with the intent of accelerating chronic wound healing, providing more and more favorable conditions for the treatment of chronic wounds [133, 137].

(1) Gelatin-Based Nanoparticle Loaded Antioxidant-Hydrogels. Gelatin-based hydrogels are being significantly utilized for biomedical and pharmaceutical purposes due to their excellent biodegradability, porosity, and biocompatibility [138]. However, gelatin with alginate, gelatin with hyaluronan, gelatin with chitosan, gelatin with sericin, gelatin with fibrinogen, gelatin with alginate and fibrinogen, and gelatin with alginate, fibrinogen, and hyaluronan are all used to increase the quality of gelatin-based hydrogels [139]. Additionally, different nanoparticles are put into gelatin-based hydrogels to increase their antioxidant activity. For example, CONPs can be combined with a variety of natural polymers to create antioxidant/anti-inflammatory hydrogels, such as gelatin, which has been widely employed as a wound dressing material due to its unique properties by numerous studies [140].

Thus, Augustine et al. [141] developed a biodegradable gelatin methacryloyl (GelMA) hydrogel patch containing CONPs to promote diabetic wound healing by scavenging free radicals and reducing oxidative stress (Figure 3). The presence of numerous inflammatory cells in diabetic wounds causes an increase in matrix metalloproteinase formation, which leads to the breakdown of biomolecules that coordinate wound-healing pathways [142–144].

Curcumin (CUR) nanoparticles have also been used traditionally as a powerful anti-inflammatory drug for wound healing for years, and they also have antioxidant, antibacterial, anticancer, and other medicinal properties [145, 146]. Thus, recently, a nanohybrid gelatin/dextran-based amphiphilic hydrogel material with curcumin and CONPs was developed by Andrabi et al. [86] for chronic wound healing applications (Figure 4).

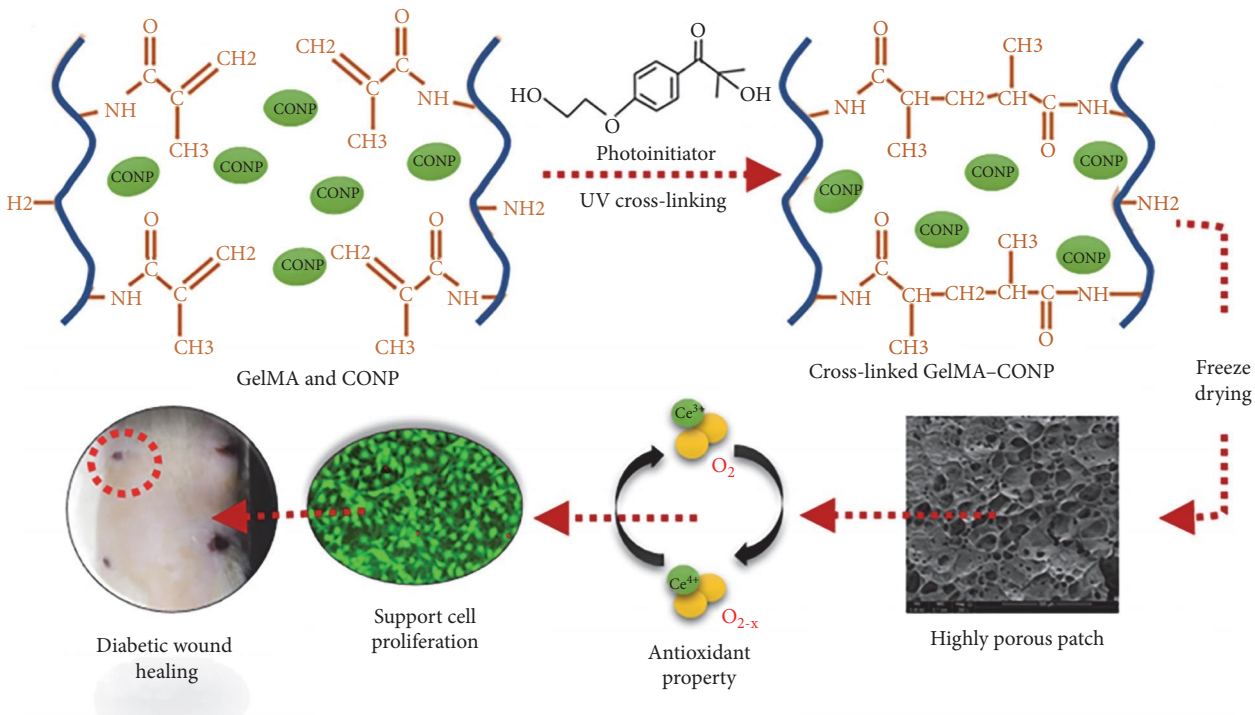

Figure 3: The diagram of GelMA hydrogel patch containing CONPs [141].

4.1.2. Antibacterial Hydrogels. During an injury, the risk of microbial contamination at the wound site rises, leading to the development of a chronic wound. Furthermore, due to the wet and nutrient-rich conditions, implants used during surgeries and biomaterials utilized in medical applications may raise the risk of bacterial infection [147]. Antimicrobial agents such as antibiotics, antiseptics, herbal therapies, and enzymes are used to minimize microbial infections at the wound site. Silver nanoparticles (Ag NPs), zinc oxide nanoparticles (ZnO NPs), and cerium oxide nanoparticles (CONPs) loaded hydrogels, for example, have long-lasting antibacterial action [148–150].

(1) Gelatin-Based Nanoparticles Loaded Antibacterial Hydrogel. Gelatin-based hydrogels loaded with AgNPs and AuNPs are being significantly utilized in biomedical and tissue-engineering applications due to their antibacterial activities. Using acrylamide (AM) and biodegradable gelatin (Gel), Reddy et al. [151] created an Ag nanocomposite hydrogel. This biodegradable poly(Gel-AM) silver nanocomposites hydrogel showed significant antimicrobial property against Gram-positive bacteria (bacillus) and hence has potential applications in wound and burn treatments [151]. In another study, Zhou et al. [152] developed a multifunctional AgNPs/phosphotungstic acid–polydopamine nanocomposite embedded in a CS/GEL biocomposite hydrogel that showed excellent antibacterial activity as well as accelerating wound healing.

Gelatin methacryloyl (GelMA) hydrogels have been utilized in a variety of biomedical applications due to their high biological qualities and physical characteristics. In the presence of photoinitiators, GelMA hydrogels have been shown to have more effective gelation reaction mechanism and contribute for better mechanical stability of hydrogel. GelMA gels have been shown to be beneficial in wound healing in several trials; thus, Jahan et al. [153] developed soft methacrylated gelatin (GelMA) hydrogels entrapped with AgNPs. This hydrogel has been shown to be a promising antibacterial scaffold for wound healing (Figure 5). It was demonstrated that cells spread more widely and moved more quickly when 15% GelMA soft gels were cross-linked with 1 min of UV irradiation. It was also proven that 10 nm AgNPs encapsulated in 15% GelMA gels release over a 72 hr time scale and display antibacterial action against Gram-positive and Gram-negative bacteria at cell-safe concentrations [153].

Lu et al. [102] developed AuNPs-loaded CS–Gel wound dressings (CS-Au@MMT/gelatin) for biomedical purposes. They initially synthesized 2-mercapto-1-methylimidazole (MMT)-capped gold nanocomposites (CS-Au@MMT) by employing chitosan (CS) as a reducing and stabilizing agent, then combined it with gelatin (Gel) and freeze dried it for the development of desired hydrogel dressing material [102]. This biocompatible wound dressing material demonstrated good mechanical qualities, effective water absorption and holding capacities, and antibacterial potential against methicillin-resistant *S. aureus*-associated wound infection [102].

(2) Cellulose-Based Nanoparticles Loaded Antibacterial Hydrogel. Although BC membranes are natural wound dressing material, they lack antibacterial activity. However, the presence of considerable number of hydroxyl groups on cellulose surface enables it to be functionalized with a wide range of nanomaterials. It is therefore recommended to functionalize BC with an antimicrobial agent in order to make it relevant in wound healing and to avoid subsequent infection. Pal

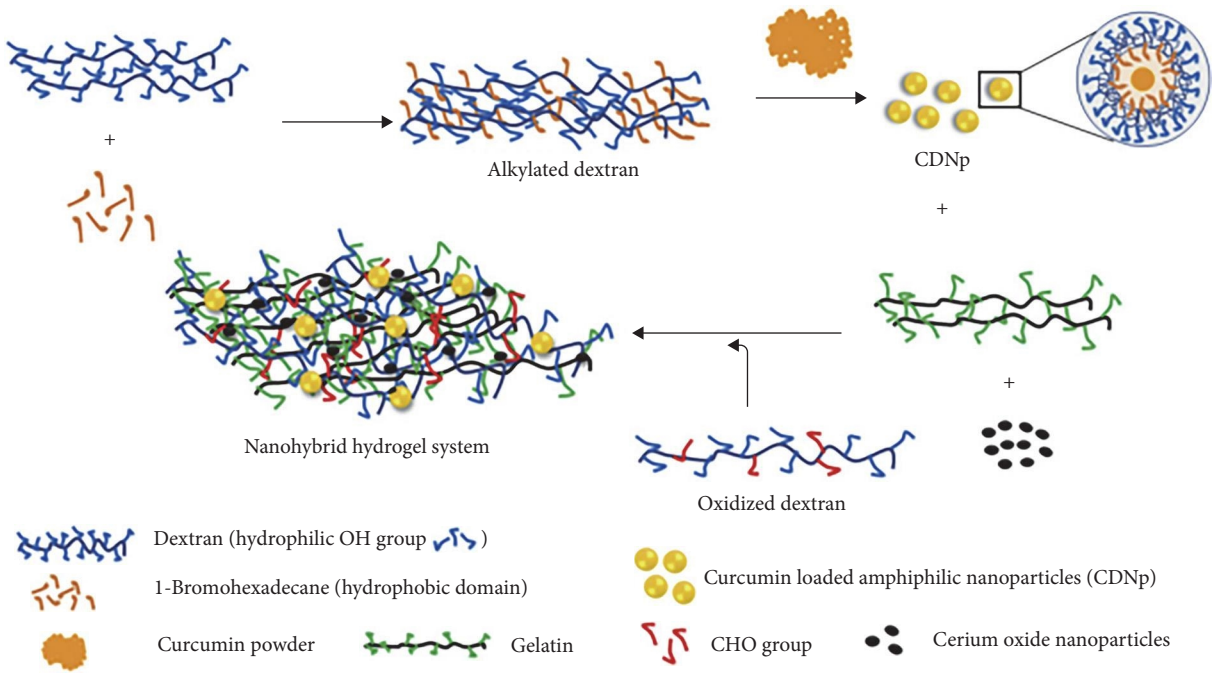

Figure 4: The production of the composite hydrogel loaded with curcumin NPs and CONPs is shown in this diagram [86].

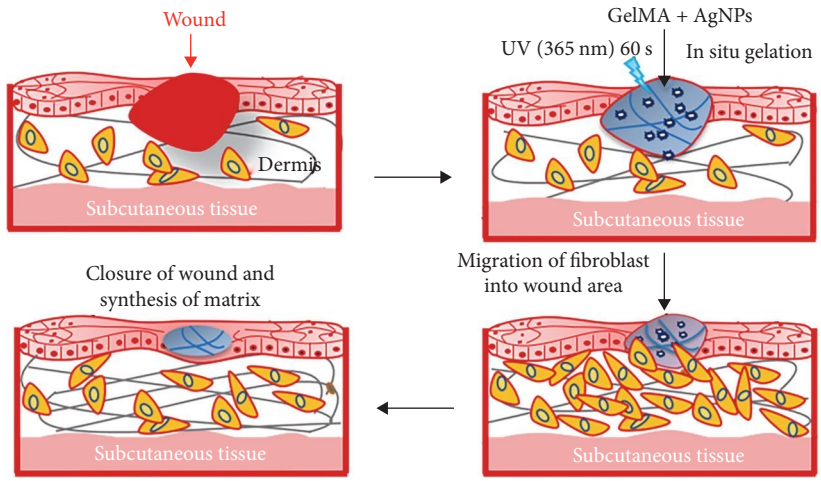

Figure 5: The hypothesized method of action of AgNPs-entrapped GelMA gels is depicted in this diagram [153].

et al. [154] coated AgNPs (size between 5 and 12 nm) on nanofibrillated bacterial cellulose (Ag/BC) using a photochemical reduction technique with UV light, and they were effective in killing Gram-negative bacteria (*E. coli*) (Figure 6).

Hydrogels made of carboxymethylcellulose (CMC) and copper oxide nanoparticles (CuONPs) were synthesized and described by Yadollahi et al. [155]. The antibacterial activity of these bionanocomposite hydrogels (CMC/CuONPs) against *E. coli* and *S. aureus* was excellent. As a result, the carboxymethyl cellulose/CuO nanocomposite hydrogels produced may be employed successfully in biomedical applications [155].

In a study, Yadollahi et al. [156] used a mixture of carboxymethyl cellulose (CMC), layered double hydroxides (LDH), and AgNPs to create antibacterial nanocomposite hydrogels (Ag/CMC-LDH). The antibacterial activity of this hydrogel was good against both types of bacteria (*E. coli* and *S. aureus*). However, due to the combined antibacterial action of Cu and Ag, the modified hydrogel (Ag/CMC-Cu-LDH) demonstrated improved antibacterial activity [156]. In a separate work, Gupta et al. [157] reported the synthesis of AgNPs-loaded BC hydrogel wound dressing that exhibited excellent antimicrobial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and Candida aureus.

(3) Chitosan-Based Nanoparticles Loaded Antibacterial Hydrogel. Li et al. [158] prepared a novel chitosan loaded with AgNPs and AuNPs (CS–Au–Ag) using egg white (Figure 7). The CS–Au–Ag hydrogels showed excellent antibacterial activity against *E. coli* and *S. aureus* bacteria and were also

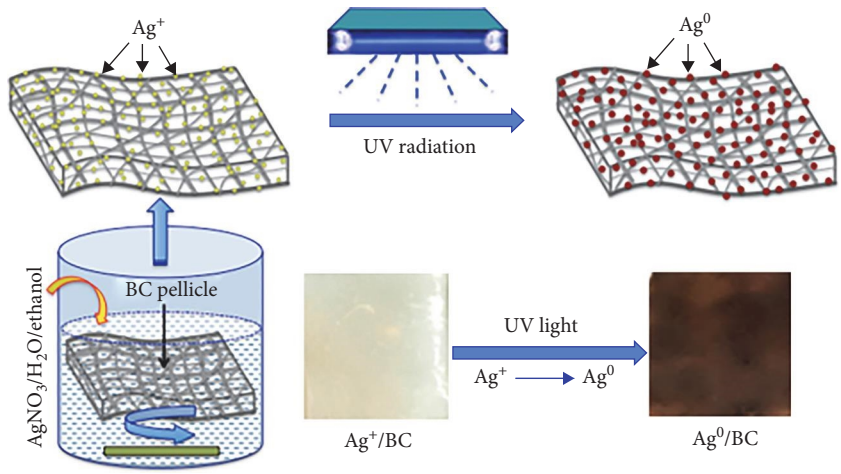

Figure 6: The synthesis of Ag/BC nanocomposite from AgNPs and BC under UV light irradiation is depicted in this image [154].

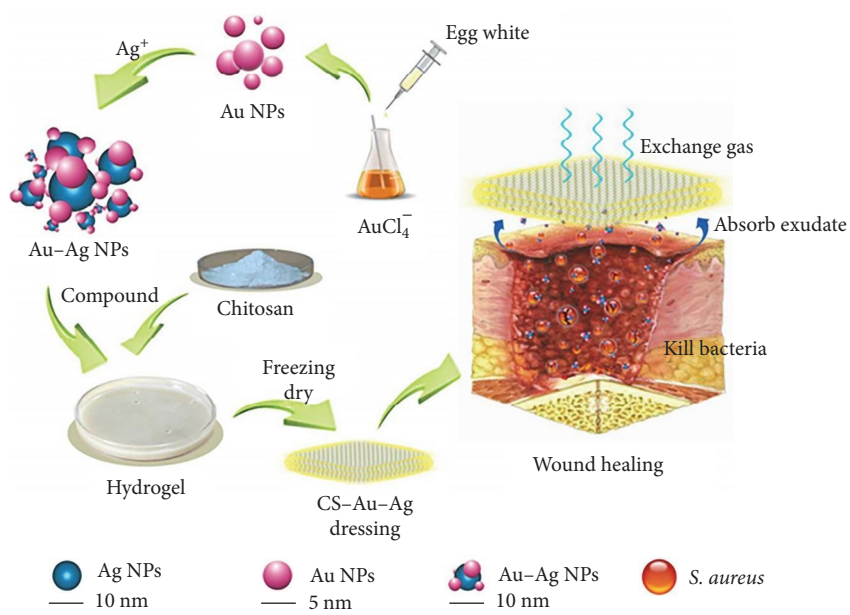

Figure 7: Conceptual illustration of the preparation for CS–Au–Ag hydrogel and thus its utilization as a wound dressing [158].

nontoxic to L929 cells [158]. Thus, CS–Au–Ag nanocomposite can be used as an effective wound dressing material due to its enhanced antibacterial activity, better mechanical properties, and high porosity.

Nonetheless, chitosan's low mechanical strength is its fundamental flaw, and blending chitosan with other polymers is one of the simplest solutions to approach this issue [159]. A wound dressing composite has been developed by Kalantari et al. [85] utilizing a green process using a PVA-chitosan hydrogel integrated with CONPs and a *Zingiber officinale* extract as a reducing, capping, and stabilizing agent. *Zingiber officinale* is an organic herb that has been utilized as a flavoring agent in a variety of beverages and foods since ancient times. The extract's major ingredient, zerumbone, is currently being utilized and researched for anticancer and antiviral activities [160]. The antimicrobial activities of the hydrogels were tested against (MRSA) as a Gram-positive bacteria and (*E. coli*) as a Gram-negative bacteria. The hydrogels containing 0.5% CONPs efficiently reduced MRSA growth, with an 85% reduction in colonization after just 12 hr, according to the findings, but did not inhibit *E. coli* colonization [85]. This hydrogel has improved swelling properties, enhanced porosity, good water absorption efficiency, and was biocompatible and nontoxic to skin fibroblasts up to 5 days [85].

Farhoudian et al. [161] used sodium tripolyphosphate (STPP) as the cross-linker and sodium hydroxide (NaOH) as the oxidizing agent to physically cross-link CuO nanoparticles (CuONPs) with chitosan (CS) hydrogel beads. In comparison to plain hydrogel, the produced nanocomposite hydrogels beads (CS/CuONPs) displayed pH-sensitive swelling behavior in several aqueous solutions and revealed strong antibacterial activities against *S. aureus* and *E. coli* bacteria and can be used for various biomedical applications [161].

The antibacterial activity of PVA/chitosan/ZnO composites has been observed to be higher than antibiotics like metronidazole and erythromycin [162]. Thus, to further improve its antibacterial activity, as a wound dressing, a PVA/CS/ZONPs/heparin hydrogel was created by Khorasani et al. [163]. Heparin has been utilized to increase the bioactivity and biocompatibility of wound dressings by acting as an anti-inflammatory and anticoagulant drug [164, 165]. The produced hydrogel had excellent mechanical strength, high water vapor permeability and swelling properties, and an increased number of pores in the hydrogel scaffold [163]. The hydrogels created have minimal toxicity and have adequate antibacterial action, particularly at high ZONP concentrations. Hydrogel had a 70% antibacterial efficacy against *E. coli* and *S. aureus* bacteria [163]. Based on the polymers (natural and synthetic) and types of nanoparticles listed in Table 1, hydrogel has been evaluated.

4.2. Films. Free-standing films have widely been used as biomaterials in wound healing, medication delivery, tissue repair, and even artificial organ regeneration [166]. Such films made of hydrophilic polymers are also biodegradable and absorbable into bodily fluids via the skin without causing any harmful effects, making them a perfect solution for the wound healing process [167]. Polymeric films are containing nanoparticles with antibacterial and antioxidant properties, such as chitosan, collagen, silk fibroin, alginate, poly(b-amino esters), and alginate sodium.

Skin inflammation (sunburn), redness, and itching can all be caused by ultraviolet (UV) light [168]. As a result, sun exposure or irradiation should be avoided all through skin wound healing process [169]. However, zinc oxide NPs (ZONPs) are more effective UV blockers than TONPs, but both ZONPs and TONPs are photosensitive and can interact with light, reducing their effectiveness or potentially causing tissue damage [170, 171]. The 3M Cavilon No Sting Barrier Coating spray is a polymeric solution that forms a homogenous film when sprayed on the skin. Thus, Lin et al. [172] added the spherical ZONPs to 3M cavilon no sting barrier coating spray due to their larger specific surface area than that of other different ZONPs shapes. The developed spray may protect wounded skin from UV irradiation, and during wound healing, 80% of Hs68 cells survive after 1 hr of UV irradiation, compared to 55% without photoprotection [172].

In another experiment, Wang et al. [173] made a chitosan (CS) film containing arginine (Arg) and gold nanoparticles (AuNPs). The CS–Arg/AuNP dressing promoted wound closure and showed exceptional antibacterial properties against *E. coli* and *S. aureus* bacteria, hydrophilic nature, mechanical strength, and biocompatibility, making the suggested film a potential option for skin tissue engineering in the near future [173].

Furthermore, using chitosan, polyvinylpyrrolidone (PVP), and silver oxide nanoparticles (AgONPs), Archana et al. [174] created a wound healing film based on chitosan (CS–PVP/AgONPs). Apart from the capacity to swell, it also has antimicrobial properties. The transparency of the film allows for regular wound monitoring without having to remove it from the wound site. It was also demonstrated that this AgONPs-loaded CS film had better wound healing properties than all chitosan-based dressings and gauze [174].

In 2020, Razali et al. [175] created the first biocompatible titanium dioxide (TONPS) loaded gellan gum (GG) biofilm wound dressing material. This (GG/TONPs) biofilm has excellent antibacterial activity against *E. coli* and *S. aureus* bacteria, as well as significant swelling and a moderate water vapor transmission rate [175].

Chen et al. [176] used strontium doped TONPs (Sr-TONPs) on CS polymer to create a biocompatible chitosan-based nanocomposite film (CS/Sr-TONPs) for wound healing applications. After 12 days, this CS/Sr-TiO_2 demonstrated a high wound healing rate of about 93% as well as good antibacterial action against *E. coli* and *S. aureus* bacteria [176]. Puccetti et al. [177] reported the synthesis of alginate-based composite films containing Ag/AgCl NPs that showed good antibacterial and antibiofilm activities. Table 2 evaluates several natural and synthetic polymer types and nanoparticles utilized in film preparation.

4.3. Sponge. Biodegradable sponge composites composed of natural polymers such as collagen, chitosan, cellulose, gelatin, and SA have a highly interconnected and porous structure, excellent elastic properties, adequate water vapor transmittance, cytocompatibility, antibacterial actions, and rapid hemostasis. Wang et al. [178] investigated the biochemical and biophysical properties of chitosan-crosslinked collagen sponge (CCCS) comprising recombinant human acidic fibroblast growth factor (CCCS/FGF) sponge in boosting diabetic wound healing. In another work, curcumin was incorporated into the chitosan (CS) and SA sponge (CA sponge) to prevent wound infection and enhance wound healing [179]. Nguyen et al. [180] prepared and tested a sponge composite comprised of two natural polymers, chitosan and gelatin, loaded with curcumin in varying quantities for wound healing applications. Wu et al. [181] fabricated a multifunctional hemostatic sponge with effective and long-lasting properties. The sponge has a complicated longitudinal staggered structure that allows red blood cells and platelets to be enriched. A series of studies also showed that the sponge has good hemostatic performance, safety, biodegradability, antibacterial properties, and the ability to enhance wound healing [181].

Liang et al. [182] prepared a sponge-like silver nanoparticles (AgNPs)/chitosan wound dressing with asymmetrical wettability that might be used to treat burn, chronic, and diabetic wound infections. This nanocomposite dressing has a high porosity, blood-clotting capacity, and increased moisture retention duration, which promotes wound healing. More significantly, antibacterial tests in vitro and in vivo show that the compound has good antibacterial activity against both drug-sensitive and drug-resistant pathogenic microorganisms [182].

Ye et al. [183] developed antibacterial sponges containing AgNPs by freeze-drying cellulose composite sponges, which exhibited outstanding antibacterial activity against *S. aureus* and *E. coli* (Figure 8). The cellulose/AgNPs composite sponges demonstrated good mechanical qualities and

Table 1: The characteristics and applications of different nanoparticle loaded hydrogel nanocomposite are discussed.

Biopolymers/synthetic polymers	Nanoparticles	Properties	Applications	References
Gelatin–methycryloyl (GelMA)	CeO_2 (CONPs)	Antioxidant, biodegradable, in vitro cell proliferation, high exudate absorption capacity, and increased porosity	Diabetic wound healing hydrogel patch	[141]
Gelatin–dextran (Gel/Dex)	Curcumin (CUR) and CeO_2 (CONPs)	Antioxidant and anti-inflammatory activities, rapid cell migration, biodegradable, and biocompatible	Inflammation-based pathology wound healing hydrogel	[86]
Acrylamide–gelatin (Gel-AM)	AgNPs	Antibacterial against Gram +, biodegradable, and higher water intake capacity	Wound and burn treatment hydrogel	[151]
Gelatin–methycryloyl (GelMA)	AgNPs	Antibacterial against Gram + and Gram −, nontoxic to cells, rapid fibroblast migration, and biodegradable	Deep dermal wound healing hydrogel	[153]
Gelatin–chitosan (CS–Gel)	AuNPs	Antibacterial against Gram +, biocompatible, high porosity, and effective water absorption capacity	MAR bacteria infected wound healing hydrogel	[102]
Bacterial cellulose (BC)	AgNPs	Antibacterial against Gram −	General and surgical wound healing dressing material	[154]
Carboxymethyl–cellulose (CMC)	CuONPs	Antibacterial against Gram + and Gram −	Different biomedical applications	[156]
Carboxymethyl cellulose–layered double hydroxide (CMC–LDH)	AgNPs	Antibacterial against Gram + and Gram −	Different biomedical applications	[156]
Chitosan (CS)	AgNPs and AuNPs	Antibacterial against Gram + and Gram −, nontoxic, high porosity, excellent mechanical properties, good swelling and retention property, and easily removable	Wound dressing material	[158]
Chitosan–polyvinyl alcohol (PVA–CS)	CeO_2 (CONPs)	Antibacterial against Gram +, nontoxic, excellent water absorption capacity, enhanced porosity, and good swelling properties	Wound dressing material	[85]
Chitosan (CS)	CuONPs	Antibacterial against Gram + and Gram −	Various biomedical applications	[161]
Chitosan–polyvinyl alcohol/heparin (PVA–CS/Hep)	ZnO (ZONPs)	Antibacterial against Gram + and Gram −, excellent mechanical strength, high water vapor permeability, and good swelling properties	Wound dressing material	[163]

Table 2: The characteristics and applications of different nanoparticle loaded films nanocomposite are discussed.

Biopolymers/synthetic polymers	Nanoparticles	Properties	Applications	References
3M cavilon no sting barrier	ZnO (ZONPs)	Highly protective against UV irradiation	Wound healing photoprotection film	[172]
Chitosan and arginine (CS–Arg)	AuNPs	Exceptional antibacterial properties against Gram + and Gram − bacteria, improved hydrophilic nature, enhanced mechanical strength, and good biocompatibility	Wound healing medication and future tissue engineering material	[173]
Chitosan—polyvinyl alcohol (PVA–CS)	AgO–NPs	Effective antibacterial activity against *S. aureus* than that *E. coli*, good mechanical properties. Excellent swelling capability	Wound healing film	[174]
Gellan gum (GG)	TiO_2 (TONPs)	Antibacterial against Gram + and Gram − and good swelling properties	Wound healing film	[175]
Chitosan (CS)	Sr–TONPs	Antibacterial against Gram + and Gram − and highly biocompatible	Wound healing film	[176]

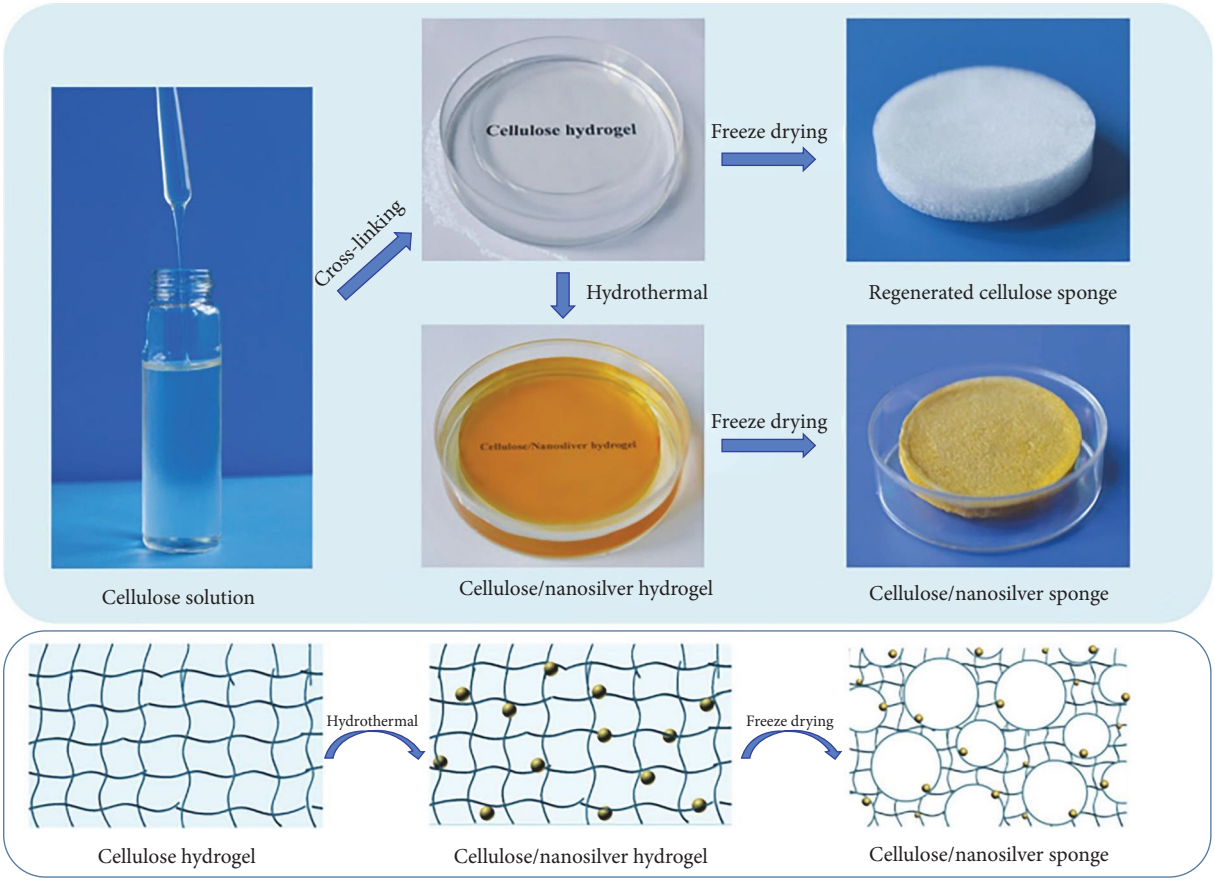

FIGURE 8: Photographs show the cellulose solution used in the manufacture of regenerated cellulose sponge and cellulose/AgNPs composite sponges (top), as well as the graphic architecture of the cellulose hydrogel, composite hydrogel, and sponge (bottom) [183].

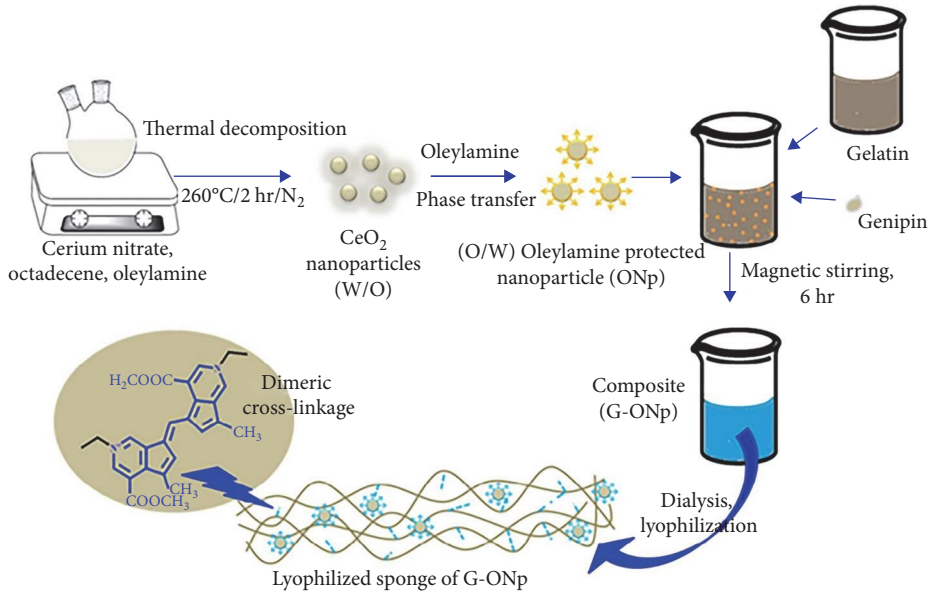

FIGURE 9: The preparation of oleylamine-protected CONPs and then creation of a cross-linked gelatin–CeO_2 composite (G-ONp) from a mixture of CONPs, gelatin, and genipin have been graphically depicted [20].

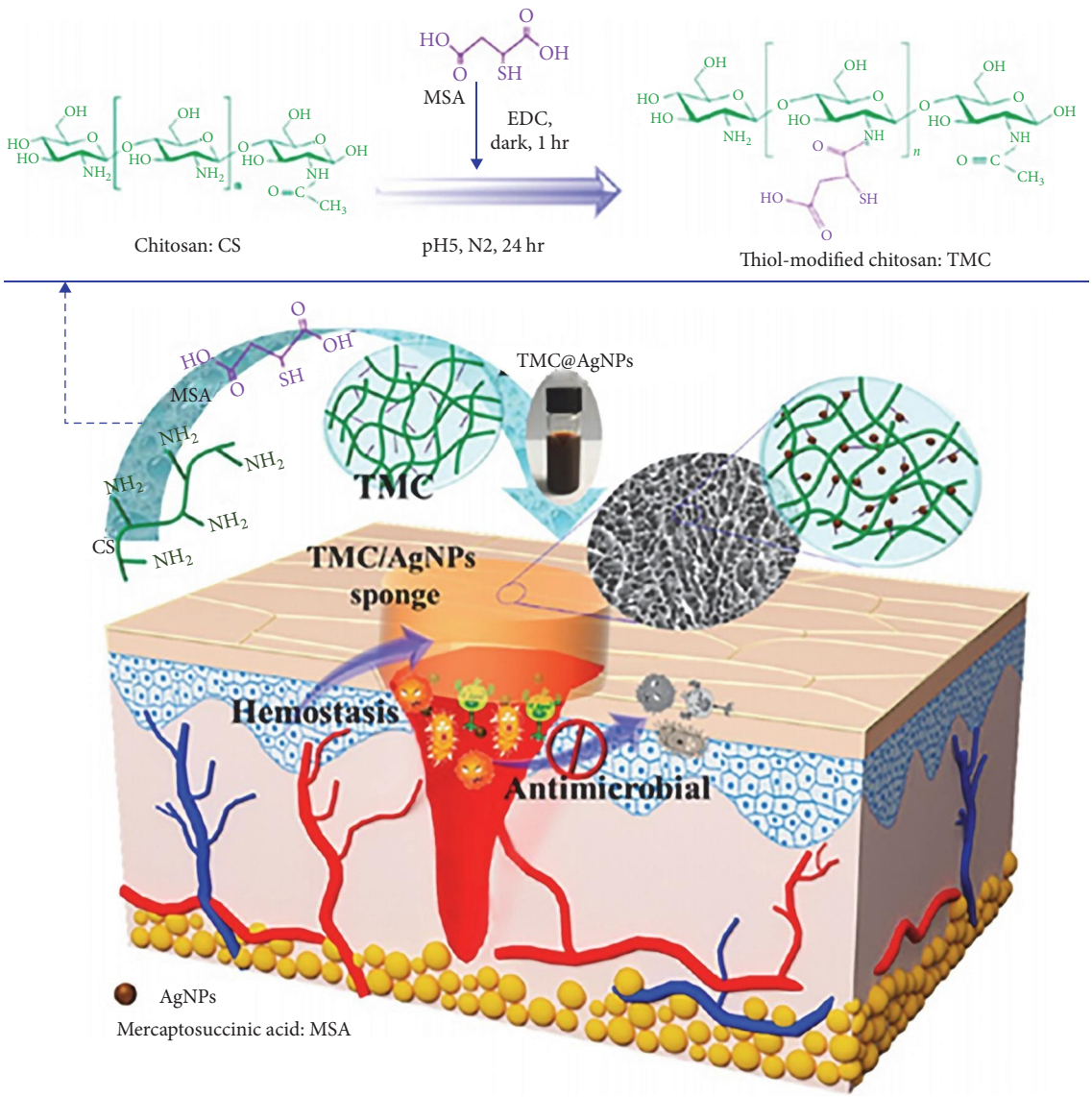

Figure 10: The manufacture and application of thiol-modified chitosan-immobilized AgNPs hemostatic sponges are depicted schematically [181].

biocompatibility, making them suitable for use in the treatment of infected wounds [183].

In another study, Raja and Fathima [20] generated a Genipin cross-linked gelatin hydrogel sponge material with an optimum concentration of cerium oxide nanoparticles (G-CONPs) for wound healing application (Figure 9). Genipin is a geniposide aglycon derived from *Gardenia jasminoides* Ellis fruits. The concentration of CONPs in G-ONPs hydrogel has been tuned to 250 g/mL, resulting in over 80% cell survival in a cytotoxicity investigation, and thus, lyophilized sponge of G-ONPs can be considered as a wound dressing material in the future [20].

Wu et al. [181] developed a multifunctional hemostatic sponge with effective hemostatic, long-lasting antibacterial activity, and great biocompatibility (Figure 10. This immobilized AgNPs composite sponge (TMC/AgNPs) based on thiol-modified chitosan (TMC) demonstrated good antibacterial activity against S. aureus, *P. aeruginosa*, and *E. coli*, as well as rapid and effective hemostatic performance [181].

Sponges based on nanoparticles made of both natural and synthetic polymers have demonstrated remarkable efficacy in wound healing applications. A few polymer–nanoparticle sponge wound dressing materials are evaluated in Table 3.

4.4. Electrospun scaffolds. The electrospinning technology may turn polymeric solutions or melts into continuous fibers with diameters as tiny as a few nanometers [184–187]. Electrospinning has recently attracted a lot of attention for the development of wound dressing scaffolds due to the relatively high permeability of the materials, as well as the presence of different pore diameters, a surface area, and a texture that is similar to the natural extracellular matrix in the skin [50, 188, 189]. Polylactic acid (PLA), PVA, polyacrylonitrile (PAN), poly(vinyl acetate) (PVAc), poly(-caprolactone) (PCL),

Table 3: The characteristics and applications of different nanoparticle loaded sponge nanocomposite are discussed.

Biopolymers/synthetic polymers	Nanoparticles	Properties	Applications	References
Chitosan (CS)	AgNPs	High porosity, excellent blood-clotting capacity, and enhanced moisture retention duration, antibacterial activity against both drug-sensitive (*E. coli* and *S. aureus*) and drug-resistant (MRSA and DREC) pathogenic microorganisms	Burn, chronic, and diabetic wound treatment	[182]
Cellulose (C)	AgNPs	Antibacterial activity against Gram + and Gram − bacteria, enhanced mechanical strength, excellent biocompatibility, high wound exudate absorption, and air permeability	Infected wounds treatment sponge	[183]
Gelatin–genipin (Gel–G)	CeO_2 (CONPs)	High porosity and swelling ratio, higher bound water capacity, and nontoxic to cells	Future wound healing sponge	[181]
Thiol-modified chitosan (TMC)	AgNPs	Antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa*, high porosity, excellent flexibility, high water absorption capacity, and good biocompatibility	Infected wounds treatment sponge	[181]

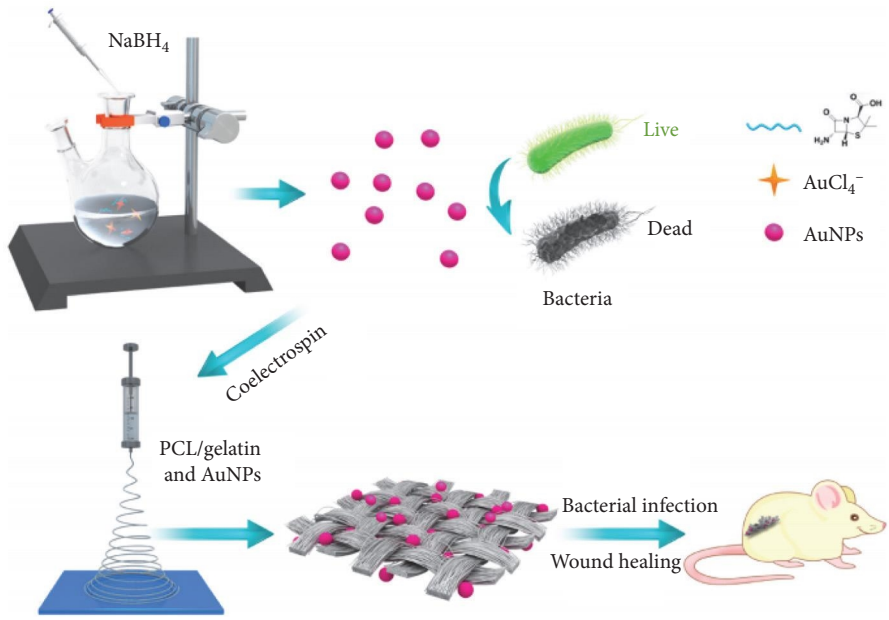

Figure 11: The synthesis of antibacterial AuNPs and their application for wound healing are depicted in this diagram [199].

chitosan, and polyurethane (PU) are indeed different types of electrospinning nanofibers that can be used as wound dressings [185, 190]. Electrospun nanofibers act as a medication delivery system for wound healing therapies (e.g., anti-inflammatory, antimicrobial agents, growth factors, drugs, and anesthetics) [191, 192]. Integrating active ingredients into electrospun fibers, such as metallic or metal oxide NPs, is a prospective way to enhance their biological functions [193, 194]. In addition, nanofibers with various 3D structures may be generated by replacing the spinnerets with various configurations (coaxial, Janus, triaxial, etc.), which frequently result in distinct drug-releasing behaviors [195].

4.4.1. Antibacterial Electrospun Nanofibers. AgNPs in electrospun nanofibers exhibit significant antibacterial activity that is useful to wound healing [196, 197]. Augustine et al. [194] reported a simple one-step electrospinning procedure for making poly(dopamine methacrylamide-co-methyl methacrylate) (MADO), an electrospun mussel-inspired copolymer with increased antimicrobial property due to surface functionalization with AgNPs. The MADO-AgNPs composite nanofibers containing 1% NPs were found to have good antibacterial action against both Gram-negative bacteria (*E. coli*) and Gram-positive bacteria (MRSA) while having no effect on mammalian cell viability. Then, Yang et al. [198] prepared Janus electrospun wound dressing composed of ethyl cellulose (EC) and polyvinylpyrrolidone (PVP) polymer matrices, in which ciprofloxacin (CIP) and AgNPs were loaded on the two sides. The Janus nonofibers were shown to have excellent antibacterial activity against the growth of both *S. aureus* and *E. coli*.

Treating a multidrug-resistant (MDR) bacterium wound infection is difficult due to the inability of traditional antibiotics. As a result, creating wound dressings for wound care, particularly against MDR bacteria, has sparked a lot of interest. Thus, using 6-aminopenicillanic acid coated AuNPs (APA-AuNPs) to prevent MDR bacteria infection, Yang et al. [199] reported an approach in wound dressing design in 2017 (Figure 11). They used the electrospun scaffold to investigate the AuNPs' antibacterial activity and wound-healing potential. The APA-AuNPs we used are bacterium resistant and have great biocompatibility. Gelatin and polycaprolactone (PCL), which are polymers loaded with the pharmaceutical ciprofloxacin (CIP) and ZONPs, were utilized by Xu et al. [200] to prepare electrospun films to be employed as potential wound dressings. Excellent antibacterial activity was demonstrated by the dressing against *S. aureus* and *E. coli*. Wang et al. [201] used polycaprolactone (PCL) and cellulose acetate (CA) polymers loaded with AgNPs and lavender oil (LO), respectively, and processed these into two-compartment Janus fibers. The obtained electrospun nanofibers demonstrated good antibacterial activity against *S. aureus* and *E. coli*.

4.4.2. Antioxidant Electrospun Nanofibers. Chronic diabetic wounds are caused by a lack of cell proliferation, cell migration, and angiogenesis. Recently, diabetes wounds are one of the leading causes of mortality and morbidity in diabetic patients, with complications including prolonged inflammation, severe infections, and wound nonclosure, leading to surgery of limbs and, in some cases, death. The use of appropriate antioxidant and anti-inflammatory medicines helps hasten the healing of diabetic wounds. Thus, electrospinning is an excellent way to build extremely porous, submicrometer-diameter antioxidant nanofibers from natural and synthetic materials.

In biological systems, CONPs have been shown to have antioxidant and enzyme-mimetic actions. Thus, Augustine et al. [202] used the therapeutic potential of CONPs for boosting diabetic wound healing, created electrospun poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) membrane-based

Table 4: The characteristics and applications of different nanoparticle loaded electrospun nanofibers are discussed.

Biopolymers/synthetic polymers	Nanoparticles	Properties	Applications	References
Poly(dopamine methacrylamide-co-methyl methacrylate) (MADO)	AgNPs	Antibacterial activity against Gram + and Gram − bacteria	Potent wound healing dressing	[194]
6-Aminopenicillanic acid (APA)	AuNPs	Antibacterial activity against MDR bacterial infection and excellent biocompatibility	Infected wounds treatment	[199]
Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)	CeO_2 (CONPs)	Excellent tensile strength, cell adhesion, and cell viability, as well as increased cell proliferation and vascularization, and excellent cytocompatibility	Diabetic wound healing	[202]
Ethyl cellulose (EC) and polyvinylpyrrolidone (PVP)	AgNPs	Antibacterial activity against *S. aureus* and *E. coli*	Wound dressing	[198]
Gelatin and polycaprolactone (PCL)	ZONPs	Antibacterial activity against *S. aureus* and *E. coli*	Wound dressing	[200]
Polycaprolactone (PCL) and cellulose acetate (CA)	AgNPs	Antibacterial activity against *S. aureus* and *E. coli*	Wound dressing	[201]

new wound covering matrices to increase cell proliferation, cell migration, and angiogenesis. In vitro cytocompatibility and cell adhesion characteristics of created membranes loaded with CONPs (particularly at 1% w/w) give positive results. The CAM test revealed that membranes loaded with CONPs increased angiogenesis and may significantly improve diabetic wound healing. Table 4 evaluates several types of natural/synthetic polymers and different nanoparticles utilized in electrospun scaffolds.

5. Conclusion and Future Directions

Millions of individuals are affected by acute and chronic wounds each year, necessitating the development and testing of therapeutic debridement and effective wound dressings. Traditional dressings such as bandages, gauzes, and cotton wool were formerly used for the healing of wounds to keep the wound clean and dry with modest exudate levels. These dressings, on the other hand, do not offer a moist environment, do not prevent microbial infections, and may adhere to the wound bed, disrupting wound healing; consequently, they have been replaced by modern dressings with more sophisticated formulas. An optimal dressing should be able to keep the wound wet and pH balanced, promote oxygen exchange, isolate proteases, stimulate growth factors, avoid infection, enable autolytic debridement, and promote granulation tissue and re-epithelialization.

In this study, we covered several advanced wound dressing perspectives such as hydrogels, films, sponges, and electrospun nanofibers loaded with various metallic and metallic oxide nanoparticles. Due to their ability to influence the development of biofilms and microbial colonization in wounds, nanoparticle-coated wound dressings play a significant role in the healing of chronic and diabetic wounds. They have also been demonstrated to have strong antioxidant and antibacterial activity.

ZONPs, CONPS, AuNPs, TONPs, and AgNPs are among the numerous metals and metal oxides that might be used in combination with biopolymers and synthetic polymers as a wound dressing. The novel chronic wound healing nanoparticle-loaded dressings are versatile systems that stimulate wound healing with minimum scar formation, reduce wound oxidative stress, cure bacterial infection, and even deliver active biomolecules encapsulated at precise rates to fit wound healing requirements. Hydrogels can be a significant adjuvant in the treatment of chronic and diabetic wounds, speeding the healing process, and lowering consequences like infections and necrosis of tissues around the wounds. In terms of antibacterial activity, Ag NPs appear to have a better antimicrobial ability than other nanomaterials, whereas CONPs have good antioxidant activity.

Thus, it is clear that using these metallic NPs can create a new therapeutic approach for treating wounds, showing strong results in reducing microbial infections, and minimizing the damage chronic inflammation causes, and speeding up the healing process. The future objective is to create nanotechnology frameworks that are reliable, controllable, well-monitored, and all FDA-approved components must be utilized. To reduce the negative effects of these nanomaterials in the human body, it is necessary to improve the production and characterization of nanoparticle-based wound healing systems with controlled nanoparticle delivery at specific wound sites. Future strategies also involve creating NPs-based dressings that combine the use of several growth factors that aid in wound regeneration and also have the capacity to penetrate biofilms, eliminate biofilms, or even stop biofilm development.

Data Availability

The authors confirm that the data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

The authors of this article confirm their contribution to the paper as follows: Mohammad Tahir Aminzai contributed to writing and correcting the original draft, revision, and editing of the manuscript; and Abubaker Patan contributed to writing the original draft, discussed the results, commented on the manuscript, and helped shape the research.

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